



Clinical trial results:

A Multicenter, Open-label, Randomized Phase 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta

Summary

EudraCT number	2019-001485-15
Trial protocol	FR RO
Global end of trial date	28 September 2022

Results information

Result version number	v2 (current)
This version publication date	10 October 2024
First version publication date	10 July 2024
Version creation reason	• Correction of full data set Global Completion Date was updated.

Trial information

Trial identification

Sponsor protocol code	MYR204
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03852433
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 September 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of bulevirtide administered subcutaneously at a dose of 2 mg or 10 mg in combination with pegylated interferon alfa-2a once weekly relative to 10 mg bulevirtide monotherapy in participants with chronic hepatitis delta.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Romania: 41
Country: Number of subjects enrolled	Moldova, Republic of: 31
Country: Number of subjects enrolled	Russian Federation: 92
Worldwide total number of subjects	175
EEA total number of subjects	52

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	174
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in France, Moldova, Romania and Russia.

Pre-assignment

Screening details:

258 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Pegylated Interferon alfa-2a (PEG-IFN alfa)
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Arm description:

Participants received PEG-IFN alfa 180 microgram (mcg) once a week subcutaneously for 48 weeks with additional 48 weeks follow-up.

Arm type	Active comparator
Investigational medicinal product name	Pegylated Interferon alfa-2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously.

Arm title	Bulevirtide 2 mg/day + PEG-IFN alfa
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Arm description:

Participants received bulevirtide 2 mg once a day subcutaneously in combination with PEG-IFN alfa 180 mcg once a week subcutaneously for 48 weeks followed by bulevirtide 2 mg once a day for 48 weeks and additional 48 weeks follow-up.

Arm type	Experimental
Investigational medicinal product name	Bulevirtide 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously.

Investigational medicinal product name	Pegylated Interferon alfa-2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously.

Arm title	Bulevirtide 10 mg/day + PEG-IFN alfa
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Arm description:

Participants received bulevirtide 10 mg once a day subcutaneously in combination with PEG-IFN alfa 180 mcg once a week subcutaneously for 48 weeks followed by bulevirtide 10 mg once a day for 48 weeks and additional 48 weeks follow-up.

Arm type	Experimental
Investigational medicinal product name	Pegylated Interferon alfa-2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously.

Investigational medicinal product name	Bulevirtide 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

Bulevertide 2*5 mg injection administered subcutaneously.

Arm title	Bulevirtide 10 mg/day
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Arm description:

Participants received bulevirtide 10 mg a once a day subcutaneously for 96 weeks with additional 48 weeks follow-up.

Arm type	Experimental
Investigational medicinal product name	Bulevirtide 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

Bulevirtide 2*5 mg injection administered subcutaneously.

Number of subjects in period 1	Pegylated Interferon alfa-2a (PEG-IFN alfa)	Bulevirtide 2 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day + PEG-IFN alfa
Started	25	50	50
Completed	17	38	45
Not completed	8	12	5
Physician decision	1	-	-
Protocol violation	-	-	1
Death	-	-	1
Pregnancy	-	1	1
Adverse event	1	1	1
Non-compliance with study drug	-	-	-
Withdrawal of consent	5	8	1
Randomized but never treated	1	-	-
Lost to follow-up	-	1	-

Lack of efficacy	-	1	-
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Number of subjects in period 1	Bulevirtide 10 mg/day
Started	50
Completed	45
Not completed	5
Physician decision	-
Protocol violation	1
Death	-
Pregnancy	-
Adverse event	1
Non-compliance with study drug	1
Withdrawal of consent	1
Randomized but never treated	-
Lost to follow-up	1
Lack of efficacy	-

Baseline characteristics

Reporting groups

Reporting group title	Pegylated Interferon alfa-2a (PEG-IFN alfa)
Reporting group description: Participants received PEG-IFN alfa 180 microgram (mcg) once a week subcutaneously for 48 weeks with additional 48 weeks follow-up.	
Reporting group title	Bulevirtide 2 mg/day + PEG-IFN alfa
Reporting group description: Participants received bulevirtide 2 mg once a day subcutaneously in combination with PEG-IFN alfa 180 mcg once a week subcutaneously for 48 weeks followed by bulevirtide 2 mg once a day for 48 weeks and additional 48 weeks follow-up.	
Reporting group title	Bulevirtide 10 mg/day + PEG-IFN alfa
Reporting group description: Participants received bulevirtide 10 mg once a day subcutaneously in combination with PEG-IFN alfa 180 mcg once a week subcutaneously for 48 weeks followed by bulevirtide 10 mg once a day for 48 weeks and additional 48 weeks follow-up.	
Reporting group title	Bulevirtide 10 mg/day
Reporting group description: Participants received bulevirtide 10 mg a once a day subcutaneously for 96 weeks with additional 48 weeks follow-up.	

Reporting group values	Pegylated Interferon alfa-2a (PEG-IFN alfa)	Bulevirtide 2 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day + PEG-IFN alfa
Number of subjects	25	50	50
Age categorical Units: Subjects			
Adults (18-64 years)	25	50	49
Geriatrics (65 – 84 Years)	0	0	1
Age continuous Units: years			
arithmetic mean	41	41	41
standard deviation	± 8.2	± 9.3	± 8.6
Gender categorical Units: Subjects			
Female	6	17	15
Male	19	33	35
Race Units: Subjects			
White	21	44	43
Asian	4	3	4
Black or African American	0	3	2
Other or More Than One Race	0	0	1
HDV RNA Units: log10 IU/mL)			
arithmetic mean	5.20	5.27	5.09
standard deviation	± 1.064	± 1.355	± 1.343
liver stiffness Units: kPa			
arithmetic mean	15.8	12.8	12.5
standard deviation	± 11.57	± 6.43	± 7.60

Reporting group values	Bulevirtide 10 mg/day	Total	
Number of subjects	50	175	
Age categorical Units: Subjects			
Adults (18-64 years)	50	174	
Geriatrics (65 – 84 Years)	0	1	
Age continuous Units: years			
arithmetic mean	40		
standard deviation	± 8.5	-	
Gender categorical Units: Subjects			
Female	12	50	
Male	38	125	
Race Units: Subjects			
White	44	152	
Asian	4	15	
Black or African American	2	7	
Other or More Than One Race	0	1	
HDV RNA Units: log10 IU/mL)			
arithmetic mean	5.45		
standard deviation	± 1.098	-	
liver stiffness Units: kPa			
arithmetic mean	12.7		
standard deviation	± 6.65	-	

End points

End points reporting groups

Reporting group title	Pegylated Interferon alfa-2a (PEG-IFN alfa)
Reporting group description: Participants received PEG-IFN alfa 180 microgram (mcg) once a week subcutaneously for 48 weeks with additional 48 weeks follow-up.	
Reporting group title	Bulevirtide 2 mg/day + PEG-IFN alfa
Reporting group description: Participants received bulevirtide 2 mg once a day subcutaneously in combination with PEG-IFN alfa 180 mcg once a week subcutaneously for 48 weeks followed by bulevirtide 2 mg once a day for 48 weeks and additional 48 weeks follow-up.	
Reporting group title	Bulevirtide 10 mg/day + PEG-IFN alfa
Reporting group description: Participants received bulevirtide 10 mg once a day subcutaneously in combination with PEG-IFN alfa 180 mcg once a week subcutaneously for 48 weeks followed by bulevirtide 10 mg once a day for 48 weeks and additional 48 weeks follow-up.	
Reporting group title	Bulevirtide 10 mg/day
Reporting group description: Participants received bulevirtide 10 mg a once a day subcutaneously for 96 weeks with additional 48 weeks follow-up.	

Primary: Percentage of Participants with Sustained Virological Response at Week 24 After the Scheduled End of Treatment (SVR24)

End point title	Percentage of Participants with Sustained Virological Response at Week 24 After the Scheduled End of Treatment (SVR24)
End point description: SVR24 was defined as undetectable hepatitis delta virus (HDV) RNA (HDV RNA value < lower limit of quantitation [LLOQ] with target not detected) at 24 weeks after the scheduled end of treatment (EOT). Analysis Population Description: Full Analysis Set is defined as all randomized participants who received at least 1 dose of study drug (Peg-IFNa and/or BLV).	
End point type	Primary
End point timeframe: 24 weeks after EOT (Week 72 for Arm A and study Week 120 for Arms B, C, and D)	

End point values	Pegylated Interferon alfa-2a (PEG-IFN alfa)	Bulevirtide 2 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	50	50	50
Units: percentage of participants				
number (confidence interval 95%)	16.7 (4.7 to 37.4)	32.0 (19.5 to 46.7)	46.0 (31.8 to 60.7)	12.0 (4.5 to 24.3)

Statistical analyses

Statistical analysis title	Statistical analysis of SVR24
Comparison groups	Bulevirtide 10 mg/day v Bulevirtide 10 mg/day + PEG-IFN alfa
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	34
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.6
upper limit	50.4

Statistical analysis title	Statistical analysis of SVR24
Comparison groups	Bulevirtide 2 mg/day + PEG-IFN alfa v Pegylated Interferon alfa-2a (PEG-IFN alfa)
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2631
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	15.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	34.2

Statistical analysis title	Statistical analysis of SVR24
Comparison groups	Bulevirtide 10 mg/day + PEG-IFN alfa v Pegylated Interferon alfa-2a (PEG-IFN alfa)
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0197
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	29.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	48.2

Statistical analysis title	Statistical analysis of SVR24
Comparison groups	Pegylated Interferon alfa-2a (PEG-IFN alfa) v Bulevirtide 10 mg/day
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7186
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.3
upper limit	11.8

Statistical analysis title	Statistical analysis of SVR24
Comparison groups	Bulevirtide 2 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day + PEG-IFN alfa
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2184
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	32.7

Statistical analysis title	Statistical analysis of SVR24
Comparison groups	Bulevirtide 10 mg/day v Bulevirtide 2 mg/day + PEG-IFN alfa
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0283
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	-20

Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.1
upper limit	-3.5

Secondary: Percentage of Participants with Undetectable HDV RNA at Week 48

End point title	Percentage of Participants with Undetectable HDV RNA at Week 48
End point description: Undetectable HDV RNA at Week 48 means undetectable (< LLOQ, target not detected) HDV RNA at Week 48. Analysis Population Description: Participants from Full Analysis Set were analyzed.	
End point type	Secondary
End point timeframe: Week 48	

End point values	Pegylated Interferon alfa-2a (PEG-IFN alfa)	Bulevirtide 2 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	50	50	50
Units: percentage of participants				
number (confidence interval 95%)	20.8 (7.1 to 42.2)	40.0 (26.4 to 54.8)	60.0 (45.2 to 73.6)	10.0 (3.3 to 21.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Undetectable HDV RNA at Week 96 (Arms B, C, and D Only)

End point title	Percentage of Participants With Undetectable HDV RNA at Week 96 (Arms B, C, and D Only) ^[1]
End point description: Undetectable HDV RNA at Week 96 means undetectable (< LLOQ, target not detected) HDV RNA at Week 96. Analysis Population Description: Participants from Full Analysis Set were analyzed.	
End point type	Secondary
End point timeframe: Week 96	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was applicable for arms B, C, and D only.

End point values	Bulevirtide 2 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	50	50	
Units: percentage of participants				
number (confidence interval 95%)	44.0 (30.0 to 58.7)	70.0 (55.4 to 82.1)	22.0 (11.5 to 36.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Combined Response at Week 24 After the Scheduled End of Treatment

End point title	Percentage of Participants With Combined Response at Week 24 After the Scheduled End of Treatment
End point description:	
Combined response was defined as fulfilment of 2 conditions simultaneously: 1) undetectable HDV RNA or decrease by $\geq 2 \log_{10}$ IU/mL from baseline, alanine aminotransferase (ALT) normalization, defined as an ALT value within the normal range, based on the central laboratories [Russian sites: ≤ 31 U/L for females and ≤ 41 U/L for males; all other sites: ≤ 34 U/L for females and ≤ 49 U/L for males]).	
Analysis Population Description: Participants from Full Analysis Set were analyzed.	
End point type	Secondary
End point timeframe:	
24 weeks after EOT (Week 72 for Arm A and Week 120 for Arms B, C, and D)	

End point values	Pegylated Interferon alfa-2a (PEG-IFN alfa)	Bulevirtide 2 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	50	50	50
Units: percentage of participants				
number (confidence interval 95%)	20.8 (7.1 to 42.2)	36.0 (22.9 to 50.8)	52.0 (37.4 to 66.3)	26.0 (14.6 to 40.3)

Statistical analyses

Statistical analysis title	Statistical analysis of Combined Response Week 24
Comparison groups	Bulevirtide 10 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0134
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	26

Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	44

Secondary: Percentage of Participants with Combined Response at Week 48 After the Scheduled End of Treatment

End point title	Percentage of Participants with Combined Response at Week 48 After the Scheduled End of Treatment
End point description:	
Combined response is defined as fulfilment of 2 conditions simultaneously: 1) undetectable HDV RNA or decrease by $\geq 2 \log_{10}$ IU/mL from baseline, ALT normalization, defined as an ALT value within the normal range, based on the central laboratories [Russian sites: ≤ 31 U/L for females and ≤ 41 U/L for males; all other sites: ≤ 34 U/L for females and ≤ 49 U/L for males]).	
Analysis Population Description: Participants from Full Analysis Set were analyzed.	
End point type	Secondary
End point timeframe:	
48 weeks after EOT (Week 96 for Arm A and Week 144 for Arms B, C, and D)	

End point values	Pegylated Interferon alfa-2a (PEG-IFN alfa)	Bulevirtide 2 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	50	50	50
Units: percentage of participants				
number (confidence interval 95%)	33.3 (15.6 to 55.3)	32.0 (19.5 to 46.7)	46.0 (31.8 to 60.7)	18.0 (8.6 to 31.4)

Statistical analyses

Statistical analysis title	Statistical analysis of Combined Response Week 48
Comparison groups	Bulevirtide 10 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0049
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	28
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.2
upper limit	45.1

Secondary: Percentage of Participants With Sustained Virological Response 48 After the Scheduled End of Treatment (SVR48)

End point title	Percentage of Participants With Sustained Virological Response 48 After the Scheduled End of Treatment (SVR48)
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End point description:

SVR48 is defined as undetectable hepatitis delta virus (HDV) RNA (HDV RNA value < lower limit of quantitation [LLOQ] with target not detected) at 48 weeks after the scheduled end of treatment.

Analysis Population Description: Participants from Full Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

48 weeks after EOT (Week 96 for Arm A; Week 144 for Arms B, C, and D)

End point values	Pegylated Interferon alfa-2a (PEG-IFN alfa)	Bulevirtide 2 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	50	50	50
Units: percentage of participants				
number (confidence interval 95%)	25.0 (9.8 to 46.7)	26.0 (14.6 to 40.3)	46.0 (31.8 to 60.7)	12.0 (4.5 to 24.3)

Statistical analyses

Statistical analysis title	Statistical analysis for SVR48
Comparison groups	Bulevirtide 10 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	34
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.6
upper limit	50.4

Statistical analysis title	Statistical analysis for SVR48
Comparison groups	Bulevirtide 2 mg/day + PEG-IFN alfa v Pegylated Interferon alfa-2a (PEG-IFN alfa)

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.8
upper limit	21.4

Statistical analysis title	Statistical analysis for SVR48
Comparison groups	Bulevirtide 2 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1247
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	-14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.9
upper limit	1.7

Statistical analysis title	Statistical analysis for SVR48
Comparison groups	Pegylated Interferon alfa-2a (PEG-IFN alfa) v Bulevirtide 10 mg/day
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1863
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	-13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.3
upper limit	5.4

Statistical analysis title	Statistical analysis for SVR48
Comparison groups	Bulevirtide 2 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day + PEG-IFN alfa
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0601
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	38.2

Statistical analysis title	Statistical analysis for SVR48
Comparison groups	Pegylated Interferon alfa-2a (PEG-IFN alfa) v Bulevirtide 10 mg/day + PEG-IFN alfa
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1265
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	42.2

Secondary: Change From Baseline in Liver Stiffness as Measured by Elastography at Week 48

End point title	Change From Baseline in Liver Stiffness as Measured by Elastography at Week 48
End point description: The mixed-effects models for repeated measurements (MMRM) model was used for analysis. Analysis Population Description: Participants from Full Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe: Baseline, Week 48	

End point values	Pegylated Interferon alfa-2a (PEG-IFN alfa)	Bulevirtide 2 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	45	47	48
Units: kPa				
number (confidence interval 95%)	-0.02 (-2.29 to 2.25)	-1.85 (-3.42 to -0.28)	-1.79 (-3.21 to -0.36)	-3.34 (-4.84 to -1.85)

Statistical analyses

Statistical analysis title	Statistical analysis Liver Stiffness Week 48
Comparison groups	Bulevirtide 10 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0717
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	3.26

Statistical analysis title	Statistical analysis Liver Stiffness Week 48
Comparison groups	Bulevirtide 2 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0875
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	0.22

Statistical analysis title	Statistical analysis Liver Stiffness Week 48
Comparison groups	Pegylated Interferon alfa-2a (PEG-IFN alfa) v Bulevirtide 10 mg/day

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0099
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-3.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.87
upper limit	-0.82

Statistical analysis title	Statistical analysis Liver Stiffness Week 48
Comparison groups	Bulevirtide 2 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day + PEG-IFN alfa
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9384
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	1.81

Statistical analysis title	Statistical analysis Liver Stiffness Week 48
Comparison groups	Pegylated Interferon alfa-2a (PEG-IFN alfa) v Bulevirtide 2 mg/day + PEG-IFN alfa
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1563
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.39
upper limit	0.71

Statistical analysis title	Statistical analysis Liver Stiffness Week 48
Comparison groups	Pegylated Interferon alfa-2a (PEG-IFN alfa) v Bulevirtide 10 mg/day + PEG-IFN alfa
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1626
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.33
upper limit	0.73

Secondary: Change From Baseline in Liver Stiffness as Measured by Elastography at Week 96

End point title	Change From Baseline in Liver Stiffness as Measured by Elastography at Week 96 ^[2]
End point description: The MMRM model was used for analysis. Participants from Full Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe: Baseline, Week 96	

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was applicable for arms B, C, and D only.

End point values	Bulevirtide 2 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	47	46	
Units: kPa				
number (confidence interval 95%)	-3.37 (-4.94 to -1.80)	-3.70 (-5.11 to -2.29)	-3.85 (-5.35 to -2.35)	

Statistical analyses

Statistical analysis title	Statistical analysis Liver Stiffness Week 96
Comparison groups	Bulevirtide 10 mg/day v Bulevirtide 10 mg/day + PEG-IFN alfa

Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8645
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	1.83

Statistical analysis title	Statistical analysis Liver Stiffness Week 96
Comparison groups	Bulevirtide 2 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5806
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.18
upper limit	1.23

Statistical analysis title	Statistical analysis Liver Stiffness Week 96
Comparison groups	Bulevirtide 10 mg/day + PEG-IFN alfa v Bulevirtide 2 mg/day + PEG-IFN alfa
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7033
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	1.39

Secondary: Change From Baseline in Liver Stiffness as Measured by Elastography at Week 144

End point title	Change From Baseline in Liver Stiffness as Measured by Elastography at Week 144
End point description: The MMRM model was used for analysis. Analysis Population Description: Participants from Full Analysis Set were analyzed.	
End point type	Secondary
End point timeframe: Baseline, 48 weeks after EOT (Week 96 for Arm A and study Week 144 for Arms B, C, and D)	

End point values	Pegylated Interferon alfa-2a (PEG-IFN alfa)	Bulevirtide 2 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day + PEG-IFN alfa	Bulevirtide 10 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	32	40	40
Units: kPa				
number (confidence interval 95%)	-0.31 (-2.75 to 2.12)	-2.35 (-4.20 to -0.50)	-2.47 (-4.12 to -0.83)	-0.79 (-2.53 to 0.93)

Statistical analyses

Statistical analysis title	Statistical analysis of Liver Stiffness Week 144
Comparison groups	Bulevirtide 10 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1103
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.75
upper limit	0.39

Statistical analysis title	Statistical analysis of Liver Stiffness Week 144
Comparison groups	Pegylated Interferon alfa-2a (PEG-IFN alfa) v Bulevirtide 2 mg/day + PEG-IFN alfa

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1533
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.88
upper limit	0.77

Statistical analysis title	Statistical analysis of Liver Stiffness Week 144
Comparison groups	Bulevirtide 2 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1526
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	3.7

Statistical analysis title	Statistical analysis of Liver Stiffness Week 144
Comparison groups	Pegylated Interferon alfa-2a (PEG-IFN alfa) v Bulevirtide 10 mg/day
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6753
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.34
upper limit	2.17

Statistical analysis title	Statistical analysis of Liver Stiffness Week 144
Comparison groups	Bulevirtide 2 mg/day + PEG-IFN alfa v Bulevirtide 10 mg/day + PEG-IFN alfa
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9124
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.28
upper limit	2.04

Statistical analysis title	Statistical analysis of Liver Stiffness Week 144
Comparison groups	Pegylated Interferon alfa-2a (PEG-IFN alfa) v Bulevirtide 10 mg/day + PEG-IFN alfa
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1129
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.98
upper limit	0.53

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: Up to approximately 144 weeks; Adverse events: Pegylated Interferon Alfa-2a (PEG-IFN Alfa): Up to Week 48 plus 30 days; for all other arms: Up to 96 weeks plus 30 days

Adverse event reporting additional description:

All-cause mortality: Participants from All Randomized Set with available data were analyzed.

Adverse events: Safety Analysis Set included all participants who took at least 1 dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Pegylated Interferon alfa-2a (PEGIFN alfa)
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Reporting group description:

Participants received PEG-IFN alfa 180 microgram (mcg) once a week subcutaneously for 48 weeks with additional 48 weeks follow-up.

Reporting group title	Bulevirtide 10 mg/Day
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Reporting group description:

Participants received bulevirtide 10 mg once day subcutaneously for 96 weeks with additional 48 weeks follow-up.

Reporting group title	Bulevirtide 10 mg/Day + PEG-IFN alfa
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Reporting group description:

Participants received bulevirtide 10 mg once day subcutaneously in combination with PEG-IFN alfa 180 mcg once a week subcutaneously for 48 weeks followed by bulevirtide 10 mg once a day for 48 weeks and additional 48 weeks follow-up.

Reporting group title	Bulevirtide 2 mg/Day + PEG-IFN alfa
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Reporting group description:

Participants received bulevirtide 2 mg once a day subcutaneously in combination with PEG-IFN alfa 180 mcg once a week subcutaneously for 48 weeks followed by bulevirtide 2 mg once day for 48 weeks and additional 48 weeks follow-up.

Serious adverse events	Pegylated Interferon alfa-2a (PEGIFN alfa)	Bulevirtide 10 mg/Day	Bulevirtide 10 mg/Day + PEG-IFN alfa
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 24 (12.50%)	2 / 50 (4.00%)	8 / 50 (16.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anaplastic astrocytoma			
subjects affected / exposed	0 / 24 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			

subjects affected / exposed	0 / 24 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 24 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 24 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 24 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 24 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	0 / 24 (0.00%)	1 / 50 (2.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 50 (2.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B reactivation			
subjects affected / exposed	0 / 24 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site cellulitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19			
subjects affected / exposed	0 / 24 (0.00%)	1 / 50 (2.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19 pneumonia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Bulevirtide 2		
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	mg/Day + PEG-IFN alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 50 (6.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anaplastic astrocytoma			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatocellular carcinoma			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic sinusitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis B reactivation			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injection site cellulitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Covid-19			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Covid-19 pneumonia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Pegylated Interferon alfa-2a (PEGIFN alfa)	Bulevirtide 10 mg/Day	Bulevirtide 10 mg/Day + PEG-IFN alfa
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 24 (91.67%)	37 / 50 (74.00%)	50 / 50 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 24 (4.17%)	0 / 50 (0.00%)	3 / 50 (6.00%)
occurrences (all)	1	0	3
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 24 (20.83%)	0 / 50 (0.00%)	13 / 50 (26.00%)
occurrences (all)	5	0	19
Asthenia			
subjects affected / exposed	3 / 24 (12.50%)	4 / 50 (8.00%)	6 / 50 (12.00%)
occurrences (all)	4	9	10
Injection site erythema			
subjects affected / exposed	0 / 24 (0.00%)	4 / 50 (8.00%)	4 / 50 (8.00%)
occurrences (all)	0	5	4
Influenza like illness			
subjects affected / exposed	10 / 24 (41.67%)	2 / 50 (4.00%)	20 / 50 (40.00%)
occurrences (all)	12	2	25
Chills			
subjects affected / exposed	0 / 24 (0.00%)	2 / 50 (4.00%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Injection site reaction			

subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 50 (0.00%) 0	4 / 50 (8.00%) 4
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 50 (0.00%) 0	1 / 50 (2.00%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2 0 / 24 (0.00%) 0	1 / 50 (2.00%) 1 0 / 50 (0.00%) 0	4 / 50 (8.00%) 4 4 / 50 (8.00%) 4
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all)	8 / 24 (33.33%) 10 3 / 24 (12.50%) 3 3 / 24 (12.50%) 3 8 / 24 (33.33%) 9 3 / 24 (12.50%) 5 2 / 24 (8.33%) 3 2 / 24 (8.33%) 3	5 / 50 (10.00%) 6 2 / 50 (4.00%) 4 1 / 50 (2.00%) 1 3 / 50 (6.00%) 4 1 / 50 (2.00%) 3 1 / 50 (2.00%) 3 1 / 50 (2.00%) 1	12 / 50 (24.00%) 14 4 / 50 (8.00%) 4 5 / 50 (10.00%) 6 10 / 50 (20.00%) 11 12 / 50 (24.00%) 19 8 / 50 (16.00%) 13 7 / 50 (14.00%) 10

Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	6 / 24 (25.00%) 8	3 / 50 (6.00%) 4	7 / 50 (14.00%) 9
Bile acids increased subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 50 (2.00%) 1	4 / 50 (8.00%) 5
Amylase increased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	3 / 50 (6.00%) 3	0 / 50 (0.00%) 0
Prothrombin level decreased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 50 (2.00%) 2	3 / 50 (6.00%) 3
Alpha-2 macroglobulin increased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 50 (4.00%) 2	3 / 50 (6.00%) 3
Lipase increased subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	4 / 50 (8.00%) 8	2 / 50 (4.00%) 2
Cardiac disorders Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	4 / 50 (8.00%) 5	2 / 50 (4.00%) 3
Angina pectoris subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 50 (0.00%) 0	1 / 50 (2.00%) 2
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	5 / 50 (10.00%) 9	2 / 50 (4.00%) 2
Headache subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	7 / 50 (14.00%) 20	7 / 50 (14.00%) 8
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	14 / 24 (58.33%) 18	8 / 50 (16.00%) 11	24 / 50 (48.00%) 35

Leukopenia subjects affected / exposed occurrences (all)	13 / 24 (54.17%) 17	8 / 50 (16.00%) 15	27 / 50 (54.00%) 46
Neutropenia subjects affected / exposed occurrences (all)	12 / 24 (50.00%) 19	6 / 50 (12.00%) 8	28 / 50 (56.00%) 45
Anaemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 50 (2.00%) 1	6 / 50 (12.00%) 8
Lymphopenia subjects affected / exposed occurrences (all)	7 / 24 (29.17%) 7	5 / 50 (10.00%) 6	15 / 50 (30.00%) 28
Eye disorders			
Presbyopia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 50 (0.00%) 0	0 / 50 (0.00%) 0
Retinal vascular disorder subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 50 (0.00%) 0	0 / 50 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	4 / 50 (8.00%) 5	4 / 50 (8.00%) 6
Dyspepsia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 50 (2.00%) 1	2 / 50 (4.00%) 2
Abdominal pain subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 50 (4.00%) 2	1 / 50 (2.00%) 1
Dry mouth subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 50 (2.00%) 1	3 / 50 (6.00%) 3
Nausea subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	3 / 50 (6.00%) 3	4 / 50 (8.00%) 4
Gingival bleeding			

subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 50 (0.00%) 0	3 / 50 (6.00%) 6
Hepatobiliary disorders			
Hepatic fibrosis			
subjects affected / exposed	1 / 24 (4.17%)	3 / 50 (6.00%)	0 / 50 (0.00%)
occurrences (all)	1	3	0
Hyperbilirubinaemia			
subjects affected / exposed	3 / 24 (12.50%)	4 / 50 (8.00%)	2 / 50 (4.00%)
occurrences (all)	4	4	2
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 24 (4.17%)	0 / 50 (0.00%)	3 / 50 (6.00%)
occurrences (all)	1	0	4
Pruritus			
subjects affected / exposed	0 / 24 (0.00%)	3 / 50 (6.00%)	5 / 50 (10.00%)
occurrences (all)	0	3	5
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 24 (4.17%)	4 / 50 (8.00%)	3 / 50 (6.00%)
occurrences (all)	1	6	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 24 (0.00%)	2 / 50 (4.00%)	3 / 50 (6.00%)
occurrences (all)	0	2	3
Myalgia			
subjects affected / exposed	2 / 24 (8.33%)	2 / 50 (4.00%)	4 / 50 (8.00%)
occurrences (all)	2	2	4
Arthralgia			
subjects affected / exposed	1 / 24 (4.17%)	1 / 50 (2.00%)	4 / 50 (8.00%)
occurrences (all)	1	1	17
Infections and infestations			
Covid-19			
subjects affected / exposed	0 / 24 (0.00%)	2 / 50 (4.00%)	5 / 50 (10.00%)
occurrences (all)	0	2	5
Urinary tract infection			

subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 50 (0.00%) 0	2 / 50 (4.00%) 2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 24 (8.33%)	1 / 50 (2.00%)	2 / 50 (4.00%)
occurrences (all)	3	2	2
Vitamin D deficiency			
subjects affected / exposed	3 / 24 (12.50%)	13 / 50 (26.00%)	13 / 50 (26.00%)
occurrences (all)	3	15	14

Non-serious adverse events	Bulevirtide 2 mg/Day + PEG-IFN alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 50 (98.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	5		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	34		
Asthenia			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Injection site erythema			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	68		
Influenza like illness			
subjects affected / exposed	22 / 50 (44.00%)		
occurrences (all)	31		
Chills			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	10		
Injection site reaction			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	28		

Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Anxiety			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Weight decreased			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Neutrophil count decreased			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	14		
White blood cell count decreased			
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	10		
Platelet count decreased			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	11		
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Bile acids increased subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Amylase increased subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Prothrombin level decreased subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Alpha-2 macroglobulin increased subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Lipase increased subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 5		
Cardiac disorders Sinus bradycardia subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Angina pectoris subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Headache subjects affected / exposed occurrences (all)	7 / 50 (14.00%) 30		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	23 / 50 (46.00%) 30		
Leukopenia			

subjects affected / exposed	26 / 50 (52.00%)		
occurrences (all)	35		
Neutropenia			
subjects affected / exposed	23 / 50 (46.00%)		
occurrences (all)	37		
Anaemia			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	6		
Lymphopenia			
subjects affected / exposed	12 / 50 (24.00%)		
occurrences (all)	24		
Eye disorders			
Presbyopia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Retinal vascular disorder			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Dry mouth			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Gingival bleeding			

subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Hepatobiliary disorders			
Hepatic fibrosis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	10		
Arthralgia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Infections and infestations			
Covid-19			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Urinary tract infection			

subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Vitamin D deficiency			
subjects affected / exposed occurrences (all)	9 / 50 (18.00%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2021	The protocol has been amended primarily to transfer sponsorship from MYR GmbH to Gilead Sciences, Inc and to update safety reporting procedures accordingly. Global changes made throughout protocol include: <ul style="list-style-type: none">• Sponsor changed from MYR GmbH to Gilead Sciences, Inc.• Contact details have been updated, including changes to safety reporting.
08 February 2022	The primary reasons for this amendment are to (1) update the regulatory and clinical development status of bulevirtide, (2) give instructions for operational changes in sample collection, and (3) specify changes to the statistical analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34482769>

<http://www.ncbi.nlm.nih.gov/pubmed/36712949>